Marta Lado *Editor*

Ebola Virus Disease

A Manual for EVD Management

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Introduction to Viral Haemorrhagic Fevers

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Colin S. Brown and Oliver Johnson

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Viral Haemorrhagic Fevers have long captured the public imagination, conjuring up images of germ warfare, biohazard suits, and national security threats. In reality, they have a wide range of clinical manifestations and propensity to cause sustained outbreaks. What is true across all of them, is a general lack of understanding of disease mechanics, an overall lack of therapeutic treatment options, and the opportunity for spread from an animal or insect host (bat, ruminant, tick, or other) into the human population.

The bunyavirus responsible for Crimea-Congo Haemorrhagic Fever (CCHF), as exemplified by its name, has the greatest geographic distribution of known VHFs,

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extending across the African continent, through Eastern Europe, the Middle East, and across to the south-east Asian subcontinent to the western edge of China. This widespread ecological niche is due to the range of the principal *Hyalomma* tick vector. Other VHFs, such as the arenavirus that causes Lassa Fever, are more limited in area, confined in this case to a few countries in West Africa where it remains endemic in rodents. The flavivirus responsible for Omsk hemorrhagic fever (OHF), is limited to muskrat population in Western Siberia. New world arenaviruses cause a variety of geographically distinct disease manifestations, such as the Machupo virus causing Bolivian haemorrhagic fever (BHF), transmitted through infected mice. The filoviruses that cause Ebola Virus Disease (EVD) and Marburg, are thought to have reservoirs in a variety of bat populations found across Africa, though most prominent in Central, East, and West Africa.

Some viruses, including those endemic in rodents and ruminant s such as those responsible for Lassa Fever and CCHF, are thought to cause a wide range of illness, from asymptomatic through a mild cold-like illness to severe disease manifestations with haemorrhagic complications and death. Others, such as types of Ebola virus including the most common Zaire strain (EBOV), are thought to near universally cause a severe illness with a very high case fatality rate if patients are left without significant, targeted supportive care.

The specific animal reservoir of Ebola virus remains unknown, though increasing evidence suggests that fruit (and likely some insect-eating) bat populations may be responsible. Bats have been demonstrated to become infected with and subsequently clear filovirus infection. Mammals such as non-human primates can be exposed an infected in identical manner to human populations, and also pose a route of introduction into a local community. The increasing nature of human ingress in natural animal habitat, coupled with food security concerns, and ease of transport both within, and between, countries and continents, means it is likely that we shall see increasing numbers of outbreaks.

EVD was first identified jointly in Zaire (now the Democratic Republic of Congo, DRC) and South Sudan in separate outbreaks with different viral subspecies in 1976.[1] Outside of a very small number of sporadic cases in the late 1970s, it was not seen, or most likely recognised, outside of a laboratory environment for the subsequent 15 years, re-emerging in Gabon in 1994. The next 20 years saw increasing numbers of outbreaks, with different species of Ebola virus (Taï Forest, Bundibugyo, and the non-human primate Reston species). The case fatality rates varied from approximately 50% to up to 90%—the largest ever seen before the West African Outbreak of 2013–2016 was in Uganda, in 2000–2001, numbering 425 cases.

The scale and severity of the 2013–2016 West African was unprecedented—by its close over 28,600 people had been affected, and over 11,300 people had died. The outbreak lasted two and a half years, involved a significant multi-agency and

[1]CDC. Outbreaks Chronology: Ebola Virus Diseases. Atlanta: CDC, 2017. Available at: https://www.cdc.gov/vhf/ebola/outbreaks/history/chronology.html

international relief effort at a cost of billions of US dollars (the US spent $2.4 billion alone in its response) to the global community,[2] and a devastating effect on the local economies of Guinea, Liberia and Sierra Leone.

1.1 Ebola

Ebola Virus is a single-stranded negative sense RNA virus, simple in its genetics, with only seven proteins encoded for. It produces its severe disease manifestation through a mixture of dysregulation of host immune function, causing endothelial damage, and direct viral effects on tropic tissues including the kidney, liver, brain, and pancreas. Ebola Virus Disease has an incubation period of between two-21 days, with the majority of infections occurring within the first 10 days. The initial symptoms are vague, such as fatigue, anorexia, fever, and general malaise, and mimicking a large number of infectious aetiologies including malaria. People subsequently develop gastrointestinal symptoms including abdominal pain, diarrhoea, vomiting and hiccups. Many progress to neurological involvement and some will develop abnormal bleeding and shock, followed by death. After entering the human population, it is transmitted through direct contact with infected bodily fluids (blood, faeces, vomit, semen) which enters the next person's body through contact with mucous membranes or breaks in skin. Management of the individual largely relies on symptomatic relief and correction of electrolyte imbalance, clotting abnormalities, and fluid resuscitation. Control within the community requires contact tracing of people in close contact with a case, with active symptom monitoring or possible quarantine; adequate diagnostics and isolation facilities; a trained public health and clinical workforce; community engagement and social mobilisation; and burial teams for safe burial of corpses. Following the 2014–2016, there remain no licensed treatment options, though there are promising signals for a few experimental treatments. Several vaccine candidates have been trialled, including one that demonstrated considerable effect in protecting contacts of EVD cases.

1.2 The Architecture of an EVD Outbreak Response

The clinical diagnosis and treatment of patients with EVD forms just one component of an overall outbreak response. This should be led by an Emergency Operations Centre (EOC), which national, donor, UN and non-governmental organisations should all work through. An Incident Manager should lead the EOC and provide oversight for the response. Several clusters, or pillars, should operate under the EOC

[2]CDC. Cost of the Ebola Epidemic: Ebola Hemorrhagic Fever. Atlanta: CDC, 2016. Available at: https://www.cdc.gov/vhf/ebola/outbreaks/2014-west-africa/cost-of-ebola.html

and these should include a configuration of: social mobilisation; surveillance; case management; laboratory services; burials; and coordination.[3]

The bedrock of an Ebola outbreak response is social mobilisation and community engagement. The public need to be informed about the virus and its transmission so that they can modify any behaviours that might put them or others at risk of infection. They also need to trust and the response, so that they agree to collaborate with it and are forthcoming with information about possible new cases. Public health messaging will be a component of this, such as radio adverts, text messaging or house-to-house visits. More critically, the response must engage with existing community structures, which may include traditional or religious leaders.

The surveillance team track the epidemiology of the outbreak and detect new cases. This may be through community-based surveillance systems, with community health workers or district health teams alert the EOC about unexplained or suspicious deaths. The surveillance team will investigate any reported cases and ensure that samples have been sent for laboratory confirmation where required. They will ensure that any close contacts of an EVD patients, who may have been exposed to the virus, are traced and monitored for the duration of their possible incubation period.

The case management team ensures the isolation and safe treatment of suspected and confirmed EVD patients. All health facilities should have robust systems in place to screen patients for EVD symptoms and to isolate in a designated room or facility. Ensuring the highest standards of infection control is an essential component of protecting health workers and preventing nosocomial transmission. One or more Ebola Treatment Unit (ETU) may need to be set up to provide separate and specialist facilities where suspected or confirmed cases can receive treatment.

The laboratory cluster ensures that diagnostic services for EVD are widely available and that testing occurs swiftly. They ensure that systems are in place for the safe packaging and transportation of samples, reliable testing, and the timely and appropriate communication of results. With the increasing availability of hospital-based or point-of-care diagnostic tests, there are now considerably more options for how to achieve this.

The burials team ensure that a safe and dignified burial is conducted for EVD patients, since unsafe burials are considered a significant route of transmission. Burials should respect local cultural practices as far as possible, whilst ensuring that they mitigate any risk of transmission from corpses. Depending on the nature of the outbreak, specific criteria must be developed for whether it is only the bodies of confirmed patients that should be included in this policy, or also suspected cases or all deaths.

Finally the coordination group should facilitate communication and collaboration between the other clusters and facilitate cross-cutting issues such as the funding, logistics and supply chain for the response.

[3] https://www.cdc.gov/Mmwr/preview/mmwrhtml/mm6339a5.htm

1.3 Critical Issues to a Successful EVD Response: Lessons from the West Africa EVD Outbreak in 2014–2015

The West Africa EVD Outbreak in 2014–2015 highlighted a set of critical and cross-cutting issues that are fundamental to a successful Ebola response.

Community Engagement The response must be something that is done with communities, rather than done to them. Too often, social mobilisation was siloed and deprioritised when it should have been front and centre and considered everybody's business. A significant challenge was the history of distrust of government and foreigners held by many communities. Another was that many people did not see the disease through a biomedical lens but through a spiritual one, and much of the public health messaging did not connect with traditional health believes. The response needs to understand these factors and address them.

Empathy What the response asked of communities and patients was often inhumane or unrealistic. This included, for example, telling parents not to touch their child who was sick and dying at home. For every policy or operational decision, responders should ask themselves the question: how would I feel, and what would I do, if this were me or my child?

Politics in the Response An EVD outbreak has profound implications for a country's economy, as well as for the reputation of Ministers and senior health officials. As a result, politics inevitably permeates decision-making. A particular challenge can be attempts to hide or cover-up the data about the outbreak, which can hugely undermine efforts by responders to contain it. It is essential that the EOC maintains transparency and is given the political space to make decisions that are based on the evidence and the agreed policy.

Health System Capacity The pre-existing capacity of the health system in West Africa was limited, which provided a weak foundation for the response. Many health facilities were overcrowded and lacked key infrastructure or supplies for infection control, such as running water or soap on the wards. Shortages of staff were often severe, and there was a particular lack of clinical supervisors such as consultant physicians or senior nurses, to ensure standards were maintained. There were not robust clinical systems in place, such as cohorting of high-risk patients or screening.

Staff Motivation and Accountability At the centre of this was the low level of motivation and accountability of the health workforce. In this context it was essential to ensure stronger morale and oversight amongst teams of health workers. This included setting out defining key roles for staff, ensuring that they were incentivised to work through hazard pay or risk allowance, introducing performance-based bonuses, and publicly acknowledging and celebrating success. Staff must also be assured that they will receive the best medical treatment if they become sick; the

successful trial of a vaccine will likely be a game-changer for reducing health worker infections and increasing their willingness to treat EVD patients.

Command and Coordination An Ebola response involves multiple moving parts, including within case management. This includes monitoring bed capacity at different units, receiving suspected cases from the community, referring EVD-positive patients to an ETU, transporting blood samples and disseminating lab results, distributing essential supplies and liaising with burial teams. Coordinating this can place a huge burden of senior clinical staff and create chaos if multiple facilities are competing for the same support services. In this situation, it is advisable to set up a dedicated Command Centre to manage this coordination and logistics.

Quarantine and Restraint A hugely controversial issue in the response was the decision to impose district and household quarantine, which had devastating impacts on the communities but was widely considered ineffective. The introduction of voluntary quarantine facilities was one promising alternative, where high-risk contacts of EVD patients could choose to isolate themselves in a safe and comfortable environment and where they could receive regular monitoring. For health facilities, a major dilemma was whether to lock patients inside isolation facilities and physically prevent them from self-discharging. Emphasis was placed in gaining consent from patients, providing quality health care and ensuring they could communicate with relatives, so that they chose to stay. However the risk of EVD patients returning to their communities or exposing others to potential infection within the health facility was often considered to great, with many health facilities deciding to lock patients inside the unit.

Maintaining General Health Services During an Outbreak Whilst the emphasis of the response was on ending the EVD outbreak, the consequences it had on general health services were devastating. Many health services closed, patients were often afraid to come to health facilities and routine vaccinations were largely suspended. As a result, the excess mortality caused by the outbreak may be more from other conditions than from EVD itself. Maintaining essential health services is therefore critical, whilst recognising that some non-essential services, such as elective surgery, may need to be suspended. This requires excellent screening and infection control, maintaining the confidence of the public and prioritising general health services in the response. Innovative public health measures should be considered; for example, the mass-administration of malaria treatment in Sierra Leone was considered a successful way to reduce malaria mortality as well as the overall number of febrile patients in the community.

1.4 Future Outbreaks

Each outbreak will be contextual, routed in a particular geography, political context, point in time, and health system. There remain many unknowns, including transmission dynamics within households, best therapeutic options, and efficacy of vaccine across different subspecies and longitudinally. The overall operational response will always be reliant of the underlying health system, with significant challenges facing low resources settings. Nonetheless, we hope this book will frame the various facets of outbreak response, with a focus on clinical and public health management, that will be useful for those facing similar challenges in the future.

Clinical Features, Case Definition and Clinical Management of Ebola Virus Disease

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The Ebola virus and the Marburg virus together form the family of Filoviridae. The Filoviruses are thread-like RNA viruses that cause fever and haemorrhagic complications. The Filoviruses cause severe disease in humans and non-human primates (gorillas, chimpanzees and monkeys) with an extremely high case fatality rate in humans ranging from 25 to 90% depending on the subtype and the availability of medical care.

The Ebola virus is relatively fragile and vulnerable to

- Chlorine
- Alcohol and formaldehyde
- Soap
- Heat

2.1 Modes of Transmission

- ***Contact with the natural reservoir or infected animals***: Humans and non-human primates can be infected after being in contact with (e.g. having touched or eaten) the unknown natural host or an infected animal. This is an uncommon way of transmission, but has to occur at least once to initiate an outbreak.
- ***Direct contact with infected body fluids of an infected patient***: Contact with blood, urine, excreta, vomit, saliva, sweat, breast milk, organs, secretions and sperm (the virus can be found in semen up to 9 months after clinical recovery) can lead to infection and this is the major mode of transmission in most outbreaks.

  Routes of infection are:
  - Oral
  - Conjunctivae
  - Mucous-membrane exposure: nose and mouth
  - Sexual unprotected intercourse
  - A break in the skin
  - A penetrating object infected with body fluids of a patient, e.g. needles or razor blades.
- ***Contact with infected corpses (human or animal)***: Bodies of deceased patients or animals that died of Ebola infection are highly contagious because of the high levels of virus in the corpses. Often traditional burial rituals consist of washing and touching the body to prepare the body to be returned to the ancestors. People touching and washing the corpse are at high risk to contract the disease and this is a well-documented, major mode of transmission.

- ***Nosocomial transmission***: Needles, syringes and material contaminated with infected fluids, can cause infections in health staff and patients. When medical items are re-used without adequate sterilization on patients attending a health facility, numerous people and health staff can get infected. If no hand washing takes place in between consulting patients, infections can spread between health staff, and from health staff to other patients. The importance of this mode of transmission has shown to vary from outbreak to outbreak.

There is no evidence so far of airborne or aerosol transmission of Ebola Virus

2.2 Incubation Period and Communicability

The incubation period for Ebola is 2–21 days. The window period between exposure and development of symptoms is thought to be a minimum of 48 h. During the incubation period the patient is infected with the virus, but is asymptomatic and is not contagious.

During the first days of symptoms the levels of the virus increases and therefore its communicability increases rapidly. If the patient doesn't manage to establish a proper immune response, then the level of the virus continues to increase until death occurs. The corpse of a patient who died of Ebola is therefore highly contagious. If the immune response is sufficient, then the level of virus decreases gradually until recovery.

2.3 Pathophysiology

Ebola replicates in various human cells. Target cells for the virus are mononuclear cells, hepatocytes and vascular endothelia cells. Mononuclear and dendritic cells (that are involved in the immune response) are the first to be infected, leading to an immune suppression. As the disease progresses parenchyma cells, like hepatocytes and adrenal cortical cells, are infected, thereby affecting the function of liver and kidneys.

Massive release of inflammatory mediators causes an increase in vascular permeability leading to shock; and disseminated intravascular coagulation, leading to coagulopathy and bleeding. The virus can finally affect almost all organs leading to multiple organ failure (MOF) and cause widespread cell death.

The immunological response in the beginning of the infection will decide how fast the virus will multiply and if the evolution will be catastrophic or towards cure. The faster the antibodies immunoglobulin M (IgM) and Ig G appear, the more chance the patient has to survive. Death or recovery normally takes place between 10 and 14 days after onset of disease.